

# Improving Treatment Effectiveness in Hypertension

**I**T is a disturbing fact that only 27% of patients with hypertension have their blood pressure (BP) controlled at normotensive levels.<sup>1</sup> This has occurred despite the availability of effective antihypertensive drug treatment. It is apparent that, unless we can improve our present methods of delivering treatment and improving compliance, we will continue to leave more than two thirds of the hypertensive population with their BP uncontrolled. This article will suggest possible reasons and remedies for this poor performance. It evaluates diet treatment, drug therapy, and interventions for improving compliance and suggests changes for improvement. They are not meant to be final recommendations. Rather, the article is intended to focus concern about the subject, to suggest some possible solutions, and to open a constructive dialogue.

## DIET TREATMENT

Most hypertensive patients are asymptomatic. Because they feel well, they are not motivated to make any drastic changes in their lifestyle. For example, weight-reducing diets in obese patients are successful only over the short term. After 3 to 5 years, almost all have returned to their previous weight.<sup>2,3</sup> Most patients do not adhere to restrictive diets for long periods.

The presently recommended approach to beginning treatment, especially in mild hypertension, is diet therapy. The most frequently prescribed dietary interventions are

weight reduction and sodium restriction. A recent trial of diet plus exercise was evaluated for the treatment of hypertension.<sup>4</sup> The diet was low in energy intake and sodium. Intensive indoctrination and motivation sessions were used to obtain compliance. The diet-exercise intervention was maintained for 1 year. At the end of that time, body weight was reduced by an average of 4.5 kg and BP had fallen by an average of 10.6 mm Hg systolic and 8.1 mm Hg diastolic. Although this antihypertensive response was significant, it would not be great enough to normalize the BP of most patients with pretreatment systolic BP greater than 150 mm Hg or diastolic levels greater than 97 mm Hg. Also, addition of various antihypertensive drugs resulted in a significantly greater fall in BP. Whether their results with diet alone could be maintained over the long-term is questionable (see the discussion of the Trial of Nonpharmacologic Interventions in the Elderly below). It is also questionable whether the intensive educational effort for maintaining the diet could be duplicated in a general practice setting.

Recently, a diet rich in fruits and vegetables and low in total and saturated fats was found to lower the BP by 11.4 mm Hg systolic and 5.5 mm Hg diastolic in hypertensive patients (Effects of Dietary Patterns on Blood Pressure trial).<sup>5</sup> The duration of the dietary intervention was only 8 weeks. All meals were prepared at the various centers to ensure compliance. The subjects ate most of their meals at the centers. Further investigation will be necessary to determine whether this diet could be effective in the usual clinical setting and over the long-term.

A longer-term trial of dietary intervention was carried out by the

Trial of Nonpharmacologic Interventions in the Elderly Collaborative Research Group.<sup>6</sup> They compared the effects of withdrawal of antihypertensive drug treatment in 4 groups of patients treated as follows: (1) low-sodium diet, (2) weight-reducing diet, (3) both diets combined, and (4) usual care (no dietary interventions). Special educational efforts were used to help gain compliance. Antihypertensive drug treatment was withdrawn 3 months after randomization, and the patients were followed up for a median of 29 months. During the initial period after withdrawal of antihypertensive drugs, normal BP was maintained in approximately 93% of patients in the 3 diet intervention groups and in 87% of the usual-care patients. However, during the succeeding months, despite continued dietary restrictions, more and more patients experienced a return of their hypertension requiring the reinstitution of drug treatment. At 29 months of follow-up, the percentage of patients receiving the low-sodium diets who remained normotensive still without drug treatment had fallen from 93% to 38%, with the trend suggesting that essentially all patients would have required drug treatment within 5 years (Figure 4 of their article). These results indicate the same problem that exists with weight-loss diets. There is loss of effectiveness over the long-term despite intensive efforts at maintaining compliance.

A meta-analysis of 28 controlled trials of low-sodium diets in hypertensive patients indicated an average decrease of only 3.7 mm Hg in systolic BP for a 100-mmol/d reduction in sodium excretion.<sup>7</sup> The average diastolic reduction of 0.9 mm Hg was not significant. By contrast, the combination drug treat-

*From the Department of Veterans Affairs, Veterans Affairs Medical Center, and Georgetown University School of Medicine, Washington, DC.*

## Fixed-Dose Antihypertensive Drug Combinations\*

Drug Combination	Brand
<b><math>\beta</math>-Adrenergic blockers and diuretics</b>	
Atenolol-chlorthalidone	Tenoretic
Bisoprolol fumarate-hydrochlorothiazide	Ziac
Metoprolol tartrate-hydrochlorothiazide	Lopressor HCT
Nadolol-bendroflumethiazide	Corzide
Propranolol hydrochloride (extended release)-hydrochlorothiazide	Inderide LA
Timolol maleate-hydrochlorothiazide	Timolide
<b>ACE inhibitors and diuretics</b>	
Benazepril hydrochloride-hydrochlorothiazide	Lotensin HCT
Captopril-hydrochlorothiazide	Capozide
Enalapril maleate-hydrochlorothiazide	Vaseretic
Lisinopril-hydrochlorothiazide	Prinzide, Zestoretic
<b>Angiotensin II receptor antagonists and diuretics</b>	
Losartan potassium-hydrochlorothiazide	Hyzaar
<b>Calcium antagonists and ACE inhibitors</b>	
Amlodipine besylate-benazepril hydrochloride	Lotrel
Diltiazem hydrochloride-enalapril maleate	Teczem
Verapamil hydrochloride (extended release)-trandolapril	Tarka
Felodipine-enalapril maleate	Lexxel

\*This partial listing is representative of currently popular combinations. ACE indicates angiotensin-converting enzyme.

ment described below lowered average systolic and diastolic BP by 22 and 12 mm Hg, respectively. It is more difficult to motivate patients to change their diet than it is to have them take medication. Diets impose a major and unpleasant change in lifestyle. When diets fail to control the BP, patients may become discouraged and discontinue diet therapy completely. For these and other reasons, drug therapy should be given preference over diet treatment.

### DRUG TREATMENT

To encourage compliance, treatment should be simple and should interfere as little as possible with the patient's usual lifestyle. Treatment should reduce the BP promptly and effectively with few or no side effects and continue to do so over the long term. The antihypertensive drugs in use today are usually well tolerated, are mostly free of serious adverse effects, and seldom cause minor side effects.

The time required from beginning treatment to control of the hypertension can be important. Patients may become discouraged by a series of ineffectual treatments. It is therefore important to control the hypertension as expeditiously as possible. Of course, no treatment should be instituted during the first

few visits so as to rule out the presence of "white coat" hypertension. However, once treatment is begun, drug titration should proceed cautiously but expeditiously to achieve BP control.

### COMBINATION DRUG THERAPY

Depending on how it is prescribed, treatment with drugs can be simple or complicated, effective or ineffective. Optimal drug therapy should meet the following criteria: effective BP control, simplicity (1 tablet once per day), safety, cost-effectiveness, and little or no interference with normal lifestyle.

Combination therapy (**Table**) is more effective than monotherapy.<sup>8,9</sup> It will control the hypertension in patients who have failed to respond to several monotherapies.<sup>8</sup> Also, doses of each component are usually lower than those required for monotherapy, which tends to minimize side effects.

A fixed-dose combination tablet (Ziac) composed of the  $\beta_1$ -blocking drug bisoprolol fumarate in doses of 2.5, 5, and 10 mg plus hydrochlorothiazide, 6.25 mg, was compared with titrated doses of amlodipine besylate or enalapril maleate, both given as monotherapy.<sup>9</sup> Goal diastolic BP ( $\leq 90$  mm Hg or

a reduction  $\geq 10$  mm Hg) was achieved in 71% of those taking the combination, 69% receiving amlodipine alone, and 45% randomized to enalapril. Adverse effects were uncommon with all drugs and were least frequent with the combination therapy). Retail cost of treatment with Ziac is approximately \$0.60 per day.

Thiazides plus  $\beta$ -blockers have until recently been the only combination drug treatment tested in long-term morbidity-mortality trials. One example is the Systolic Hypertension in the Elderly Program,<sup>10</sup> in which treatment consisted of chlorthalidone, to which atenolol could be added if needed to achieve goal BP ( $\leq 160$  mm Hg systolic). At the 5-year visit, 69% of the treated patients achieved goal BP with either diuretic alone or the combination with  $\beta$ -blockers. Stroke and cardiovascular complications were significantly reduced in the drug treatment group.

Several combinations of a calcium channel blocker and an angiotensin-converting enzyme (ACE) inhibitor are commercially available. Fixed-dose combinations of diltiazem hydrochloride and enalapril maleate<sup>11</sup> were compared with monotherapy in a trial involving 891 hypertensive patients. Two dose levels of diltiazem hydrochloride were tested, 120 and 180 mg, each combined with 5 mg of enalapril maleate (Tagem). After 12 weeks of treatment, the reduction of diastolic BP averaged 7.6 and 8.3 mm Hg below pretreatment BP with the low- and high-dose diltiazem combinations, respectively, which was a significantly greater reduction than with either drug given alone. Adverse reactions were no more frequent with the combinations than with the single drugs. Similar results were observed in another trial that used a combination of benazepril hydrochloride and amlodipine.<sup>12</sup>

Recently, 2 large trials used a calcium channel blocker to which an ACE inhibitor or other drug was usually added. Treatment was effective in both trials in preventing cardiovascular events. The Syst-Eur Trial<sup>13</sup> used nitrendipine in patients with isolated systolic hypertension. Their results were similar

to those of the Systolic Hypertension in the Elderly Program. The other trial (Hypertension Optimal Treatment trial) studied the effects of different levels of diastolic BP reduction on cardiovascular morbidity and mortality.<sup>14</sup> They found that reductions below 90 mm Hg were optimal. No additional benefit occurred below 85 mm Hg. The calcium channel blocker used was felodipine. Both of these trials used titration of doses not only of the primary drug but also of the added drugs. This makes the therapeutic program more complicated than the simple fixed-dose combination. Such complexities may make treatment less successful in the real world.

A diuretic was included in the Ziac combination described previously because it is the most effective of all drugs in enhancing the antihypertensive activity of other agents. This was demonstrated in a Veterans Affairs randomized trial in patients whose BP remained greater than 140/90 mm Hg after 2 successive monotherapies.<sup>8</sup> They were then assigned in a randomized double-blind manner to various 2-drug combinations. All possible combinations of 6 major classes of drugs were tested. The combinations that included a diuretic achieved a systolic BP less than 140 mm Hg in 77% of patients and a diastolic BP less than 90 mm Hg in 69%. Combinations containing drugs other than a diuretic were less effective, even including the combination of an ACE inhibitor and a calcium channel blocker. The response rates to the thiazide combinations were impressive considering that these were patients with treatment-resistant hypertension whose BP had failed to normalize with 2 consecutive monotherapies.

Despite their reputation, diuretics have not demonstrated serious toxic effects in the various clinical trials on prevention of morbidity and mortality.<sup>15,16</sup> Furthermore, thiazides when used in combination are effective in small doses, which further minimizes the occurrence of side effects.

Other fixed-dose combinations include enalapril maleate, 5 or 10 mg, with hydrochlorothiazide, 12.5 or 25 mg, and a combination

of the angiotensin II receptor antagonist losartan potassium, 50 mg, with hydrochlorothiazide, 12.5 mg.

In the Veterans Affairs trial described previously,<sup>8</sup> the ACE inhibitor–diuretic combination lowered the BP from a pretreatment mean of 156/100 mm Hg to 134/88 mm Hg. In another Veterans Affairs cooperative study, hydrochlorothiazide, 25 mg twice daily, plus captopril, 12.5 mg 3 times daily, reduced the average diastolic BP by 16.6 mm Hg, a reduction to normal levels in nearly all patients.<sup>17</sup>

Combinations with a diuretic plus an ACE inhibitor should be useful in the presence of a variety of comorbid conditions involving the heart and kidneys. The ACE inhibitors reduce mortality both during myocardial infarction<sup>18</sup> and in the post-myocardial infarction period.<sup>19</sup> They also reduce left ventricular remodeling, which often occurs after myocardial infarction.<sup>20</sup> Both ACE inhibitors and diuretics markedly benefit patients with congestive heart failure,<sup>21,22</sup> and they are both effective in reducing left ventricular hypertrophy associated with hypertension.<sup>23</sup>

In the kidneys, ACE inhibitors significantly reduce the microalbuminuria often associated with hypertension.<sup>24</sup> The ACE inhibitors lower intraglomerular BP, thereby slowing the progression of glomerular fibrosis,<sup>25</sup> including that occurring in diabetic nephropathy.<sup>26</sup>

Many physicians are reluctant to increase doses of antihypertensive drugs to effective levels. A recent survey found that 82% of physicians failed to increase doses when indicated.<sup>27</sup> Fortunately, the diuretic combinations with a  $\beta$ -blocker or ACE inhibitor produce a high response rate with the initial doses, and only a single step-up is provided for patients who require additional medication. The mode of administration is simple: 1 tablet once daily of the weaker strength, and if the BP does not fall to normal, switch to 1 tablet per day of the second strength. The ACE inhibitors do not interfere with sexual activity or with cognitive functions. They do not induce weakness or fatigue or cause orthostatic hypotension. Small doses of diuretics probably also do not. The

combination, therefore, is not only highly effective, it is also very well tolerated.

## COMPLIANCE

Noncompliance is probably the major cause of failure to control hypertension, yet it is usually the most neglected. It is difficult to motivate asymptomatic patients in apparently vigorous good health to take medication every day for indefinite periods. Most of them are not concerned about the risk of complications that may possibly occur far in the future.

To help overcome their lack of interest, risk factors must be clearly stated and repeatedly emphasized. While the physician should lead this educational effort, most of it can usually be delegated to knowledgeable and motivated nurses or social workers. Educational materials should also be provided, including pamphlets and video programs such as those available from the American Heart Association or the National High Blood Pressure Education Program.

Attention also must be paid to side effects that can cause patients to drop out of treatment. Whenever a new treatment is initiated, the major side effects should be discussed and the patient assured that, if any should occur, another treatment will be substituted.

There has been little research on compliance in the treatment of hypertension. The few published controlled studies suggest that compliance is improved by suitable interventions. In one study, 400 patients were randomly assigned either to various compliance-promoting interventions or to no intervention.<sup>28</sup> Three compliance-promoting interventions were used: (1) a 10-minute interview and counseling session by the physician at the time of initiating treatment, (2) enlisting a member of the patient's family to monitor pill taking and other compliance matters in the home, and (3) several group sessions led by a social worker. The patients were followed up for 5 years. All-cause mortality was 57.3% less in the experimental group than in the control patients. The BP was controlled in

65% of the experimental group compared with only 22% of the controls.

In another trial, a hypertension educational program was carried out in 2 rural counties in Kentucky.<sup>29</sup> A neighboring county that had no educational program served as the control. A hypertension registry was developed. Patients in the intervention counties received periodic mailings concerning the various risks associated with hypertension and the importance of treatment in preventing complications. This information was reinforced by local newspaper articles and radio programs. Lectures were given to local nurses on the importance of teaching compliance to their patients. At the end of 5 years of follow-up, the percentage of patients in the intervention group whose BP was controlled below 140/90 mm Hg increased from 24.8% to 39.7% ( $P < .001$ ). There was no significant change in the control group. Cardiovascular risk factors were reduced in the 2 intervention communities and were increased in the control county. However, these and other studies<sup>30</sup> have excited little interest in the problem of compliance.

Home recording of BP is another procedure that is used not only to promote compliance but also as a guide in adjusting dosage. The BP is taken once or twice daily by the spouse or the patient and a record is kept of the date, time, and level of BP. Increased motivation is provided by making the patient an active partner in the process of controlling the BP. The patient also can see that persistent treatment is necessary for maintaining the BP at normotensive levels. However, some patients become upset with any upward fluctuations in BP. If they cannot accept that such fluctuations are normal, home recordings should be discontinued.

One controlled trial that tested the effectiveness of home BP recordings found that, after self-BP recordings were instituted, compliance rose from 65% to 81%,<sup>31</sup> a significant increase compared with the control group. In another trial, randomly selected patients recorded their BP at home.<sup>32</sup> These patients showed a sig-

nificantly greater degree of compliance than the control group. In a third trial,<sup>33</sup> patients who were known to be poor compliers either were randomized to usual clinic care or were asked to record their BP at home and to adjust dosage according to the readings. Compliance was improved in the home BP group as judged by pill counts and clinic attendance. Results of these studies are encouraging. However, larger-scale controlled trials are needed to more adequately evaluate this method.

Care of patients by specially trained nurses has been advocated in the treatment of hypertension<sup>34,35</sup> and diabetes.<sup>36</sup> Increased compliance has been claimed to result from this procedure. More time can be spent with each patient than the physician can usually spare. The nurse can emphasize the need for faithful compliance to the regimen and can reiterate the importance of BP control in the prevention of complications. Of course, the effectiveness of such a program will depend on the dedication and competence of the nurse.

Haynes et al<sup>37</sup> reviewed a number of control trials that tested various interventions for improving compliance. They included 5 trials in hypertensive patients. Four of the 5 trials found statistically significant (although not great) improvement in compliance in the intervention groups. The most effective interventions included single daily dosage, patient education regarding risk reduction, use of nurses in education, reinforcement and monitoring compliance by the spouse, self-measurement of BP, and support groups. Despite significant improvement with such programs, there were still many failures.

The Canadian Coalition for Blood Pressure Prevention and Control established a national advisory committee on compliance in the management of high BP.<sup>38</sup> They reported that estimates of patients' noncompliance rates vary widely in different surveys but average about 50%, including dropouts.<sup>39</sup> They present 4 recommendations for improvement: (1) education of patient and family in the importance of risk reduction, with self-measurement of BP

in nonadherent patients; (2) once-daily dosage and simplified treatment regimens; (3) having nurses review with patients their compliance status at each visit; and (4) using less expensive medications when possible. Noncompliance is the most important remaining problem in the treatment of hypertension. It needs more attention and research funding than it currently receives.

## CONCLUSIONS

Despite the availability of a variety of effective antihypertensive drugs, BP is controlled in fewer than one third of hypertensive patients. Since present methods of treatment appear inadequate, they need to be changed. The currently popular monotherapy aimed at treating comorbid conditions as well as reducing BP has not achieved the goal of normalizing the BP in an acceptable percentage of patients.

Fixed-dose combination tablets, such as diuretic- $\beta$ -blockers or diuretic-ACE inhibitors, confer much higher response rates. They provide a simple 1-pill once-daily regimen that facilitates compliance while the low dose of each component minimizes side effects. The diuretic-ACE inhibitor combination also provides treatment against many of the comorbid conditions frequently associated with hypertension.

In addition, moderate exercise should be encouraged, not only because it may produce further modest fall in BP but also because it reduces the risk of coronary heart disease.<sup>40</sup>

Other compliance-promoting procedures that have proved useful include (1) repeated emphasis on prevention of risk factors by clinic personnel in addition to pamphlets, video presentations, etc; (2) giving nurses more responsibility for follow-up; (3) enlisting the help of the patient's spouse or other family member in monitoring daily pill taking; and (4) recording the extent of noncompliance by having the pharmacist report the time intervals between refills.

Success in obtaining increased compliance has been claimed for the use of BP recording in the home. Favorable results have also been

reported for the use of specially trained nurses to act as primary caregivers for patients with hypertension. The problem of compliance has also been recognized and discussed in the Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.<sup>41</sup>

The management of noncompliance is difficult, time-consuming, and sometimes frustrating, but it appears to be most important for improving the effectiveness of treatment. We should at least attempt to improve on the present unacceptably high percentage of patients whose BPs are not controlled. To accomplish this, we must be willing to try various approaches that may prove more effective than the procedures used at present.

Edward D. Freis, MD  
Hypertension Research Clinic  
151E  
Veterans Affairs Medical Center  
50 Irving St NW  
Washington, DC 20422

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